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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Peter Svete

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EXAMINER

RAO, SAVITHA M

ART UNIT

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1614

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/590,889	Applicant(s) SVETE ET AL.	
	Examiner SAVITHA RAO	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 18 and 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 & 18-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The advisory action sent out by the examiner on 03/16/2010 is hereby withdrawn due to new grounds of action set forth below. All the claims submitted by the applicant on 03/09/2010 are entered and will be reexamined.

The notice of appeal, filed 03/9/2010, is moot in light of the new grounds of rejection summarized below

Claims 1-10 and 18-19 are pending. Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 03/09/2010 is acknowledged. Claims 1, 7 and 18 are amended and are under consideration in the instant office action.

Applicants' arguments, filed 03/09/2010 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 recites a pharmaceutical composition according to claim 1 which is in the form of a coated tablet.

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Applicants have amended the instant claim 1 upon which claim 5 depends on to recite "a pharmaceutical composition comprising a tablet core". It is noted that the tablet core can reasonable only be a core if it is coated in some way and therefore the "coated tablet" limitation of claim 5 does not further limit the already claimed tablet core which is coated recited in instant claim 1.

Claim Rejections - 35 USC § 103

New grounds of rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

It is noted that the Antoncic et al (US 7271269) used in the 103(a) rejections set forth in office actions dated 03/10/2008 and 09/30/2008 was disqualified as a prior art reference for purposes of any alleged "obviousness" rejection by operation of 35 U.S.C 103 (c) by the applicants. That reference is withdrawn from use in the 103 (a) rejection.

The instant rejection set forth below uses the WIPO document of Antoncic et al. (WO 2004/066997) in the following rejection and it is noted that this reference (WO 2004/066997) additionally qualifies as prior art under another subsection of 35 U.S.C. 102 (a), and therefore, cannot be disqualified as prior art under 35 U.S.C. 103(c).

Claims 1-10 and 18-19 and are rejected under 35 U.S.C. 103(a) as being unpatentable over to Antoncic et al. (WO 2004/066997) in view of WHO drug information(WHO drug information Vol.16, (4), 2002, pages 1-12) as evidenced by Maggi et al. (European Journal of pharmaceutics and Biopharmaceutics, 48, 1999, pages 37-42) further in view of Bharatarajan et.al. (US 2006/0177498)

Antoncic et al. discloses crystalline and amorphous potassium salts of Losartan and pharmaceutical compositions comprising them (abstract). Antoncic et al. discloses that it is known that Losartan potassium exists in at least two polymorph forms Form I

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and Form 2 (page 4, 2nd paragraph) and further discloses other references which teaches Losartan form III, Form IV and Form V (page 5, 2nd paragraph) (*reads on instant claims 1 and 2*). Antoncic et al. discloses a potassium salt of losartan characterized by a powder X-ray diffraction pattern with peaks at about 2θ 6.9, 13.8, 20.6, 24.8, 28.7, 29.2° (Form X) (page 24, 3rd paragraph) and pharmaceutical composition containing polymorphic forms of losartan specifically the form exhibiting strongest diffractions at around 2θ 6.9, 13.8, 20.6, 24.8, 28.7, 29.2° (Form X) (page 29, 1st and 2nd paragraph) (*reads on instant claims 4*). Antoncic et al. discloses an aspect of their invention where in the pharmaceutical active ingredient of the composition is the amorphous form of losartan (page 31, 3rd paragraph) or a crystalline form of Losartan (page 31, last paragraph) and film coated tablet formulations of potassium salt of Losartan wherein tablet cores with a mass of 160 mg comprising excipients such as lactose, microcrystalline cellulose, starch and aerosil was prepared and coated (page 29, 3rd paragraph and page 30, 5th paragraph) (*reads on the composition comprising a tablet core wherein the tablet core comprises an active pharmaceutical" limitation of instant claim 1 and instant claim 5*). The examples 50, 52a and 52b disclosed by Antoncic et al. describe the coated tablet formulations of polymorphic forms of potassium salt of Losartan (pages 66-70). Antoncic et al. teaches the inclusion of silicified microcrystalline cellulose in the tablet core at 40% of the total weight of the composition and film coating comprising ethyl cellulose in the concentration of 1.95% or stearic acid at 0.6% weight of the composition (see below) (examples 52a and 52b). The following table lists the taught excipients along with the %weight in each formulation,

Antoncic Example 52a	Weight, mg	Component weight %/ finished dosage form
Losartan potassium (core)	100 mg	29.74
Silicified Microcrystalline Cellulose (core)	199.2 mg	40.0
Silica colloidalis anhydrica (core)	3.2 mg	0.95%
Ethylcellulose (coat)	6.54 mg	1.95%
Finished dosage weight total (plus 0.22 mg of talc)	336.22	
Antoncic example 52b		
Losartan potassium (core)	100.00 mg	29.74
Silicified Microcrystalline Cellulose (core)	19932 mg	40
Silica Colloidalis Anhydrica (core)	1.6 mg	
Stearic acid (coat)	2.1 mg	0.6
Finished dosage weight total (plus 0.22 mg of talc)	336.22	0.5

reference to the finished dosage weight as shown in the above table yields 0.95%.

Antoncic discloses that Losartan is used as an effective drug for the treatment of hypertension (Page 1, last paragraph, page 32, 2nd paragraph 1) and additionally, discloses that the pharmaceutical composition of his invention can be in a form suitable for peroral or parental application and is indicated for treating hypertension in addition to

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teaching that his compositions can be embodied in the form of tablets, capsules etc.

(Page 29, 2nd paragraph) (*reads on instant claims 18-19*).

With respect to the limitation in instant claim 1 wherein “the pharmaceutical ingredient which exists in a first polymorph form susceptible to interconversion into one or more other polymorph forms” Antoncic et al. teaches the potassium salt of Losartan with the X-ray diffraction pattern as instantly claimed. As such the pharmaceutical ingredient taught by Antoncic et al. is the same as that instantly claimed. The compounds and its characteristics of properties cannot be separated. . Since the reference teaches the instantly claimed pharmaceutical composition comprising the instantly claimed compound which is the “potassium salt of Losartan” , which possess the instantly claimed crystal structure with identical X-ray diffraction patterns as taught by applicant it necessarily follows that it the compound will possess these properties which is the ability to exist in the first polymorph form susceptible to interconversion into one or more other polymorph forms” alleged by Applicant, absent factual evidence to the contrary. “Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).Office lacks laboratory facilities to test the prior art compounds and compositions. It is incumbent upon applicants to provide data demonstrating that the properties of the disclosed prior art compounds/compositions are different from the claimed compositions.

Antoncic et al. do not teach the exact concentration of the stabilizer instantly claimed which is between 1-10% by weight of the composition and does not teach the specific anhydrous silicon dioxide of the Syloid form instantly claimed.

However, WHO drug information document teaches Silicas (silicon dioxide) as being widely used in the manufacture of pharmaceuticals, cosmetics and food products where they are used as an adsorbent, anticaking agent, glident, suspending agent, tablet disintegrant and viscosity-increasing agent and teaches "colloidal Anhydrous silica (BP) and colloidal silicon dioxide (USPNF) and silica colloidalis anhydrica (PhEur) as trivial names and chemical names adopted by different pharmacopeias (page 3 under Silicas and beginning of page 4).

Maggi et al. is used here as evidence to demonstrate that Syloid 244 is nothing but colloidal silicone dioxide used as one of the excipients (page 38, right column, 4th paragraph). As such the prior art provides ample suggestions and teachings to demonstrate that Syloid is the same as the colloidal anhydrous silica used in the formulation of Antoncic et al. and would therefore possess similar properties.

In addition, Bharatarajan et al. teach the use of Syloid AL-1 claimed in Instant application as one of the suitable excipients with low moisture content that prohibit uptake of moisture and provide the effect of increased stability of formulations with low water contents excipients [0016, 0025-0026]. Bharatarajan et al. teach a tablet formulation of Ramipril in Example 3, comprising the active ingredient, microcrystalline cellulose at 53.9% by weight of the total composition and precipitated Silicon dioxide (Syloid) at 4.8% by weight of the total composition and further teach that the

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compositions of example 3 did not show any significant degradation over 4 weeks at accelerated testing conditions [0036-0037] .

With reference to the concentration of the stabilizer claimed in the instant claims at 1-10%, Antoncic teaches his composition to comprise 0.95% and Bharatarajan et al. teach their composition to comprise about 4.8% of silicon dioxide which renders the stabilizer weight of 1-10%, claimed in instant claims obvious. In addition, Inclusion of anhydrous silicon dioxide in tablet formulation for stability purposes is taught in the art and as such, it would be within the skill of an ordinary artisan to be able to modify the weight ratio of the excipients in order to obtain the desired stability and bioavailability profile of the active drug. It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With respect to the inclusion of Syloid silicon dioxide in the formulation as instantly claimed in claims 9-1, The art teaches that Syloid silicon dioxide instantly claimed is the same as colloidal anhydrous silica taught by Antoncic et al. Accordingly, it would have been obvious to an ordinarily skilled artisan to utilize the registered traded mark version of the colloidal silicone dioxide in the formulation as one of the type of colloidal anhydrous silica taught by Antoncic et al. Syloid silicon dioxide is a functional equivalent of colloidal anhydrous silica used by Antoncic et al. and it is further taught to function well as a stabilizer.

As such an ordinarily skilled artisan would be motivated to utilize Syloid silicone dioxide as a stabilizer in the formulation of Antoncic et al. as an equivalent replacement to the colloidal silica Anhydrica. Substituting equivalents, namely silicon dioxide, motivated by the reasonable expectation that the respective species will behave in a comparable manner or even provide comparable results in related circumstances, see *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) is *prima facie* obvious. Moreover, the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious, see *In re Font* 213 USPQ 532. Due to the fact that Bharatarajan et al. teach and provide the skilled artisan with the necessary motivation to use a Syloid silicon dioxide in a drug compositions such as tablets, and Antoncic et al. teach a formulation of Losartan comprising anhydrous colloidal silicon dioxide, one having ordinary skill in the art is clearly provided with direction and ample motivation to utilize Syloid silicon dioxide in the method of Antoncic et al and at the concentration used by Bharatarajan et al. as Syloid silicone dioxide and colloidal silica Anhydrica are functional equivalents.

Accordingly, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because it would have been *prima facie* obvious to the skilled artisan to substitute known equivalents in a pharmaceutical formulation with a goal of achieving same or better effect.. Selection of excipients and the amounts to be used can

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be readily determined by one of ordinary skilled in the arts based upon experience and consideration of standard procedures and reference work in the field.

The experimental data disclosed by the applicant (Specification pages 11-15) to demonstrate the properties of the claimed composition is noted and acknowledged. Data presented demonstrates the intrinsic stabilizing property of anhydrous finely divided silicon dioxide and cannot be used to overcome the instant rejection.

Response to applicant's arguments filed on 03/09/2010:

In light of the new grounds of rejection above, the arguments submitted on 03/09/2010 which was for the previously submitted rejection is moot.

Conclusion

Claims 1-10 and 18-19 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614